Malignant Melanoma Metastatic to Oligodendroglioma: Case Report and Literature Review of Tumor-to-Tumor Metastasis to Gliomas

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Abstract

Tumor-to-tumor metastasis is an uncommon phenomenon, and a metastasis from an extracranial donor tumor to an intracranial recipient tumor is extremely rare. In particular, there are only 14 cases reported in the literature that describe a tumor-to-tumor metastasis involving a glioma. We present a rare case of an 83-year-old man with an 11-year history of lentigo maligna melanoma who presented with impaired balance and cognitive slowing and was found to have rapid progression of a previously known indolent right frontal brain mass. Pathologic examination of the tumor after resection revealed the presence of both malignant melanoma and an oligodendroglioma WHO grade II. To the best of our knowledge, this is the first reported case of malignant melanoma metastasizing to an oligodendroglioma that has been confirmed by immunohistochemistry and genetic analysis.

Key Words: Melanoma, Oligodendroglioma, Tumor-to-tumor metastasis.

INTRODUCTION

Tumor-to-tumor metastasis is a rare phenomenon that should not be confused with a collision tumor. Collision tumors occur when 2 cancers that are histologically distinct are located in the same anatomical region and invade one another (1, 2). By contrast, tumor-to-tumor metastasis occurs when cells from a primary cancer, the donor, spread to a secondary pre-established malignancy, the recipient.

Case

An 83-year-old left-handed Caucasian man with a history of lentigo maligna melanoma, a right frontal brain lesion, and atrial fibrillation presented with a 2-week history of impaired balance and cognitive slowing with staring spells.

Eleven years prior, the patient was diagnosed with lentigo maligna melanoma on his forehead (0.7 mm) and upper back (1.1 mm). Both lesions were removed with wide resection. On biopsy of the forehead lesion, the melanoma was 0.52-mm thick with radial and vertical growth both present. There was no evidence of tumor infiltrating lymphocytes or neurovascular invasion.

Seven years prior to the current presentation, a noncontrast enhancing 2.5 cm × 2.1 cm × 2.5 cm (anterior to posterior × superior to inferior × right to left) mass in the right parasagittal
posterior frontal lobe cortex was incidentally discovered on MRI when evaluating for brain anoxia after cardiac arrest (Fig. 1A). Due to the patient’s cardiac comorbidities, the non-enhancing radiographic appearance, and the asymptomatic nature of the mass, the decision was made to manage the suspected low-grade neoplasm by observation. The lesion was monitored with annual CT scans, as MRI was contraindicated due to pacemaker placement, and the lesion slowly increased in size by $\frac{14}{24}$ mm (anterior to posterior) total over the next 7 years (Fig. 1B, C).

At current presentation, the patient had developed weakness over a period of 2 weeks. His family noted that he had difficulty ambulating, multiple falls, and delayed response to questioning. On physical examination, he demonstrated bilateral intention tremor with left-handed predominance, decreased strength in his left upper extremity with orbiting around the left arm, and a positive Romberg test suggestive of impaired proprioception. A CT scan was performed to evaluate the known intracranial lesion. The findings showed interval enlargement of the previously nonenhancing known mass within the right superior frontal gyrus, now measuring 3.9 cm x 3.7 cm x 2.8 cm with new peripheral enhancement, increased hypodensity centrally, a small area of hyperdensity along the inferior aspect concerning for hemorrhage, and extensive surrounding edema in the right frontal white matter with mass effect and midline shift (Fig. 1D, E). These morphologic changes were concerning for transformation of the presumed right frontal low-grade glioma.

The patient subsequently underwent a right frontal craniotomy for tumor resection without complication. Intraoperative pathology from the frozen specimen was suggestive of metastatic melanoma whereas the final pathology report identified 2 histologically distinct neoplastic cell types coexisting within the tumor. First, malignant melanoma was identified by the presence of malignant epithelioid cells forming nests and sheets with abundant mitotic figures (Fig. 2A). The histology of the primary lentigo maligna melanoma was similar to the metastasis, with nests of large epithelioid cells. Second, oligodendroglioma was identified by the presence of hypercellular brain infiltrated by cells with round nuclei and perinuclear halos. There were no anaplastic features seen, but clusters of melanoma cells were present within the glial lesion (Fig. 2B).

The histologic diagnosis was supported by subsequent immunohistochemical staining and genetic analyses. Immunohistochemistry showed that the melanoma component stained positive for microphthalmia-associated transcription factor (MITF) (Fig. 2C) and negative for BRAF V600E mutation. The primary skin specimen was negative for BRAF V600E by immunohistochemistry. Additional immunohistochemistry revealed that the oligodendroglioma showed positive nuclear and cytoplasmic staining for isocitrate dehydrogenase (IDH1) R132H point mutation, retained nuclear expression of ATRX, and scattered tumor cells positive for p53 (Fig. 2D–F). Ki67 labeling index was <3% in the glioma. Fluorescence in situ hybridization (FISH) showed 1p/19q codeletion, diagnostic for oligodendroglioma.

In addition, a solid fusion assay was performed to look for fusion transcripts for targetable genes, as well as further molecular analysis to look for single nucleotide variants. Single nucleotide variants of unclear significance were found in BRAF, TERT promoter, CIC, TP63, BRCA2, and MAP2K1 (Table 1). Of note, melanoma was separated from the...
oligodendroglioma by microdissection prior to the molecular testing.

Postoperatively, the patient underwent restaging scans, which demonstrated metastases in the liver, peri-pancreatic region, left adrenal gland, peritoneum/mesentery, retroperitoneum, pelvic musculature, and additional brain metastases. Subsequent treatment was focused on management of the widely metastatic melanoma. He received fractionated radiation to the resection cavity for the residual tumor and pembrolizumab, a humanized monoclonal antibody that acts as an immune checkpoint inhibitor by targeting programmed cell death 1 (PD-1) receptor. Restaging scans performed 3 months postoperatively showed systemic and intracranial disease progression despite radiation and systemic treatment with pembrolizumab. The patient was transitioned to hospice care and died 5 months postoperatively.

**DISCUSSION**

Tumor-to-tumor metastasis is a very rare but increasingly recognized entity, defined as a primary tumor metastasizing to a second histologically distinct primary tumor. Criteria have been proposed to identify tumor-to-tumor metastases and distinguish them from collision tumors: (1) the tumor must be a true neoplasm, (2) the tumors must be histologically distinct, (3) a metastatic tumor focus enclosed
within the recipient tumor must be present to rule out direct contiguous spread between 2 neoplasms, and (4) transition zone from one tumor to the other is present (2, 23, 24). The case presented here meets all of the above criteria. Both tumors were confirmed using IHC and genetic analysis as 2 distinct and true neoplasms. On pathology, malignant melanoma was identified enclosed within the oligodendroglioma.

The largest review of the literature for tumor-to-tumor metastasis of the CNS was performed by Erdogan et al in 2013 (3). This review included 114 cases of metastatic cancer within a meningioma. The most common primary tumors that metastasized to meningiomas were breast (47%) and lung (20%). He also reported metastases to other benign CNS tumors including pituitary adenoma (19 cases), hemangioblastoma (16 cases), schwannoma (11 cases), cavernoma (3 cases), paraganglioma (1 case), neurofibroma (1 case), and infundibular choristoma (1 case). A 2012 review by Moody et al that contained 84 case reports and 3 original cases also found the most common cancer to metastasize to another neoplasm was breast (62%) and the most common intracranial recipient was meningioma (2). Meningioma is the most common recipient of metastatic spread likely due to a combination of factors, including higher incidence rate compared with other brain pathologies, slow growth, highly vascular nature, and minimal host immune response within the tumor (3, 6).

While tumor-to-tumor metastasis involving gliomas are exceptionally rare, we have found 14 cases described in the literature (Table 2) in addition to the case presented here (11–22). In 1972, Farnsworth et al reported a case of a 45-year-old woman found on autopsy to have metastatic melanoma to her adrenal gland, lung, and an oligodendroglioma (14). However, the diagnosis of oligodendroglioma was made based on appearance of the cells surrounding the metastatic melanoma with hematoxylin and eosin (H&E) staining. No immunohistochemical or genetic studies were done to confirm the diagnosis of glioma. In fact, Mork et al questioned the accuracy of diagnosis of oligodendroglioma given the lack of these studies in the Farnsworth et al case, as intracerebral melanoma can appear similar to glioma (18). Therefore, in this article, we present the first case of malignant melanoma metastasizing to an oligodendroglioma that has been confirmed by genetic analysis and immunohistochemistry.

Tumor-to-tumor metastasis of melanoma to an intracranial neoplasm has been described previously in 6 cases, including 4 cases of metastases to meningiomas, and single cases of metastasis to a glioma and a central neurocytoma (4, 6, 14, 25–27). This is perhaps a surprisingly low number given the high rate of melanoma metastasizing to the brain (28–30). According to the Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review for 2014, the incidence of melanoma of the skin was 25.23 per 100,000 people and prevalence in the United States was 1,169,351 people (31). A recent large population-based study of patients diagnosed with cancer from 1973 to 2001 in the Metropolitan Detroit area using the SEER database found that 6.9% of patients with melanoma developed brain metastases (28). For comparison, prevalence of breast and lung cancer in 2014 was 3,346,387 and 527,228, respectively (31). Estimates show that 5.1% of patients with breast cancer and 19.9% of patients with lung develop brain metastases (28). Patients with advanced stage melanoma had the highest incidence of brain metastases compared with other advanced stage cancers. An increased incidence of gliomas in patients with melanoma, compared with the general population, has also been reported in the literature and is speculated to be due to genetic predisposition (32, 33). Axelsen et al studied gene expression differences between normal tissue and cancer that originated from these tissues. Interestingly, it was found that melanoma contained the highest number of normal brain selective genes, which could possibly contribute to the high rate of melanoma metastasizing to the brain (34). The relatively high number of normal brain selective genes found in melanoma could be due to the fact that both melanocytes and glial cells originate from neural crest cells.

The mechanisms underlying the metastasis of extracranial tumors to intracranial intrinsic lesions are unclear. Neoplasms in the brain have general features that may contribute

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### TABLE 1. Genetic Variants of Melanoma as Detected by Standard Testing

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Gene</th>
<th>Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligodendroglioma</td>
<td>1p/19q</td>
<td>co-deletion</td>
</tr>
<tr>
<td>Melanoma</td>
<td>CIC</td>
<td>p.Ser1272LeufsTer29 insertion</td>
</tr>
<tr>
<td></td>
<td>TERT</td>
<td>hg19 chr5: g.1295250C&gt;T; c.-146C&gt;T; C250T</td>
</tr>
<tr>
<td></td>
<td>BRAF</td>
<td>p.Arg444Gly; p.Val600Lys insertion</td>
</tr>
<tr>
<td></td>
<td>TP63</td>
<td>p.Cys95Gly</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>p.Ser1001Ileu</td>
</tr>
<tr>
<td></td>
<td>MAP2K1</td>
<td>p.Lys64Glu</td>
</tr>
</tbody>
</table>

Melanoma specimen was separated from oligodendroglioma by microdissection prior to molecular testing.

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### TABLE 2. A List of Cases of Tumor-To-Tumor Metastasis to Gliomas

<table>
<thead>
<tr>
<th>Type of Glioma</th>
<th>Origin of Metastasis</th>
<th>Author and Year of Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligodendroglioma</td>
<td>Melanoma</td>
<td>Farnsworth, 1972 (14)</td>
</tr>
<tr>
<td></td>
<td>Breast carcinoma</td>
<td>Strang, 1965 (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tally et al, 1988 (12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wurm et al, 1994 (13)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Colon carcinoma</td>
<td>Mizutani, 1987 (15)</td>
</tr>
<tr>
<td></td>
<td>Thyroid carcinoma</td>
<td>Posnikoff et al, 1960 (16)</td>
</tr>
<tr>
<td></td>
<td>Renal carcinoma</td>
<td>Franke et al, 1990 (17)</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Bronchial carcinoma</td>
<td>Mork et al, 1988 (18) (2 cases)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tajika et al, 1990 (19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tanboon et al, 2014 (20)</td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Breast carcinoma</td>
<td>Muller et al, 1999 (21)</td>
</tr>
<tr>
<td>Fourth ventricle ependymoma</td>
<td>Bronchial carcinoma</td>
<td>Mork et al, 1988 (18)</td>
</tr>
<tr>
<td>Glioma, unspecified</td>
<td>Carcinoma</td>
<td>Joglekar et al, 1981 (22)</td>
</tr>
</tbody>
</table>

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to the development of tumor-to-tumor metastasis. The blood-tumor barrier is hypothesized to be more permeable than the blood-brain barrier and brain tumors—especially gliomas that include oligodendrogliomas—are highly vascular tumors (35–37). Oligodendrogliomas have a network of interconnecting and branching capillaries, often referred to as a “chicken-wire pattern” (38). Low-grade oligodendrogliomas, as in the case presented here, have been shown to have higher cerebral blood volume compared with low-grade astroglial tumors (39, 40). In addition, higher grade oligodendrogliomas have been shown to have higher cerebral blood volume compared with lower grade oligodendrogliomas (39, 41). The increased blood-tumor permeability and the increased blood flow to a neoplasm in the brain could contribute to seeding existing oligodendrogliomas with metastases from other cancers. Further studies are needed to determine the mechanisms underlying the ability of such metastases to occur.

Although tumor-to-tumor metastases from systemic malignancy to intrinsic brain tumors are rare events, they may provide clinically important information related to diagnosis, treatment, and prognosis. In patients undergoing surveillance of indolent low-grade gliomas, the differential diagnosis of rapid enlargement or development of new enhancement should include tumor-to-tumor metastasis in addition to tumor progression or development of secondary high-grade glioma, especially in patients with another known malignancy. It is also possible that a tumor-to-tumor metastasis reflects a genetic transformation in the systemic donor malignancy that could guide therapeutic decision making and carry prognostic value. Additional studies evaluating the tumor genetics and patient outcomes in patients with tumor-to-tumor metastasis would be necessary to test for these associations.

In conclusion, we have presented the first reported case of an immunohistochemically and genetically confirmed tumor-to-tumor metastasis of malignant melanoma to an oligodendroglioma and reviewed the current literature regarding metastases to gliomas. Although tumor-to-tumor metastases are relatively rare, they should be considered in the differential diagnosis of a patient presenting with a sudden change in an indolent intrinsic brain lesion, especially if the patient has a history of metastatic cancer.

REFERENCES

11. Strang RR. METASTASIS OF A BREAST CARCINOMA TO AN INTRACEREBRAL OLIGODENDROGLIOMA. Zentralblatt Fur Neurochirurgie 1965;25:206–10